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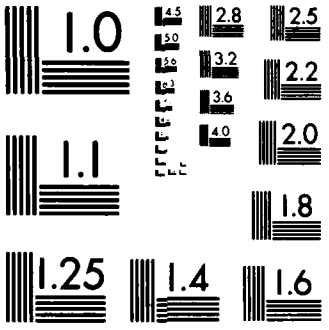

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PULMONARY ADAPTATION TO HIGH ALTITUDE

ANNUAL PROGRESS REPORT - YEAR 06
(October 1, 1982 - August 1, 1983)

Jerome A. Dempsey, Ph.D.

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20. ABSTRACT (Continue on reverse side if necessary and identify by block number)

The work accomplished during the 6th year of our contract was aimed at determining the contribution of pulmonary and chest wall mechanics to the ventilatory response to exercise and exercise in hypoxia; the effects of long-term hypoxia and of exercise in normoxia and hypoxia on respiratory muscle metabolism and morphology in the rat; and the effects of long-term hypoxia and different levels of hypoxia on ventilation and periodic breathing during sleep in hypoxia.

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The following major accomplishments are noted:

1. Exercise-induced hypoxemia in healthy persons occurs with a significant incidence during submaximal exercise solely because of an underdetermined ventilatory response and during very heavy maximal exercise occurs as a result of <u>both</u> an excessive A-aDO_2 and an absence of hyperventilation.

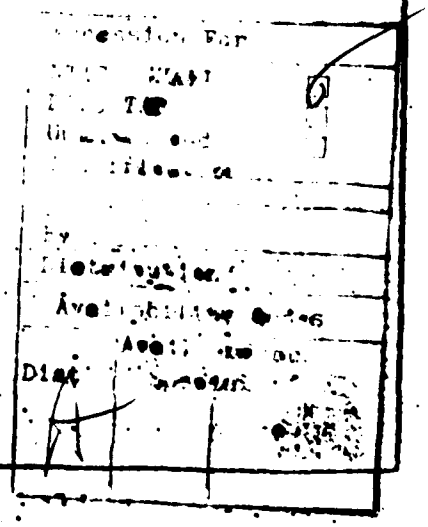
2. The variability among subjects in hyperventilatory response to heavy exercise was <u>not</u> explained on the basis of either variations in chemical stimuli (PaO_2, [H+]) or the resting ventilatory response to these imposed stimuli. Exercise-induced hypoxemia was shown to cause the appearance of yet additional potential stimuli to ventilation in the form of increasing adrenergic amines--particularly norepinephrine.

3. Heavy exercise in hypoxia caused tidal breath flow-volume curves to exceed the maximum FVC; and maximum inspiratory esophageal pressures often exceeded or matched those achieved during the MBC. During helium breathing, V_E always increased, the maximum flow- and pressure-volume loops expanded and the tidal breath during heavy or maximum exercise was within the limits of these loops.

4. During moderate to heavy exercise, inspiratory effort or "drive" increased out of proportion to inspiratory flow or V_E. This increased mechanical impedance during exercise uncouples ventilatory response from drive and the augmented drive appears to represent a load compensation even in the healthy individual. Breath-by-breath analysis during changing gas densities in exercise confirmed this "load-compensation" hypothesis.

5. The rat appears to be a good model for the study of respiratory muscle metabolism during exercise and in chronic hypoxia. Studies on both of these topics are near completion--with the data clearly indicating a strong similarity in metabolic acid production between respiratory and locomotor limb muscles in their exercise response.

6. Data analysis of breathing periodicity in hypoxic sleep was completed, with the key mechanisms centering around a highly sensitive hypocapnic-induced apneic threshold during sleep. Long-term hypoxia (4 days) did <u>not</u> cause more periodic breathing and was often coincident with less periodicity. Long-term ventilatory acclimatization was not affected by "state" (awake through non-REM and REM) and the acute (or chronic) ventilatory response to hypoxia during wakefulness or sleep did not predict the severity of periodic breathing in the sojourner at 4300 m.



ANNUAL PROGRESS REPORT

(Year 06 - October 1, 1982 to August 1, 1983)

Studies completed during contract year 06 were aimed at defining: a) the mechanical status of the lung during exercise and exercise in hypoxia and determining the role of mechanical "constraint" vs chemical drive in determining exercise ventilation and gas exchange in humans; b) determining the effect of exercise and of chronic hypoxia on respiratory muscle metabolism (in the rat); and c) determining the effects of duration of hypoxic exposure and the magnitude of hypoxic response on ventilation and periodic breathing during sleep. In general we accomplished most of our specific objectives although the human exercise studies were much more difficult than anticipated and thus we fell short of our goals in some respects. The animal exercise studies are on schedule in that most experiments are completed; however, most of the biochemical assays are yet to be done. The planned sleep studies were almost all completed and analyzed. We had a particularly productive year in synthesizing our data, in completion of manuscripts and in publishing our findings. Thus, we enclose the most relevant manuscripts which are either in press or in the review process. These papers provide many of the details of this report and we have summarized these and additional findings below.

SUMMARY OF PROGRESS TO DATE

I. Exercise Studies in Humans

A. Our analysis of exercise-induced hypoxemia in healthy, fit people is now (finally) complete and the manuscript recently submitted for publication is enclosed (Dempsey et al., 1983). To briefly summarize our previous reports, we found that significant hypoxemia (-20 to -35 mmHg $\Delta Pa\overline{O}_2$) occurred in over one-half of 16 subjects at high work loads ($\dot{V}O_2 \geq 4$ L,min), that this hypoxemia occurred in the initial 60 min of heavy exercise and was either sustained or worsened as exercise was continued over four minutes and that hypoxemia was usually accompanied by extreme alveolar to arterial $\overline{P}O_2$ differences and almost always by an absence or a very minimum of alveolar hyperventilation ($PaCO_2$ < 3 to 4 mmHg below resting levels) (see example in Fig. 1A).

Our most recent analysis of these data also revealed three additional important characteristics of those subjects who experienced severe hypoxemia in heavy exercise. First, we observed a significant incidence of hypoxemia during even moderate exercise (50 to 60% of max $\dot{V}O_2$). This was due almost entirely to a reduced ventilatory response (i.e. $A\text{-}a\overline{D}O_2$ was near-normal) and occurred only during short-term exercise, i.e. < 5 min. During long-term, submaximal exercise (60-80 min) in the same subjects at the same relative work intensity, hypoxemia rarely occurred as hyperventilaion was much more pronounced and $P_A\overline{O}_2$ substantially increased (at the same $A\text{-}a\overline{D}O_2$) (see Table 1). Potential "extra-stimuli" to hyperventilation during long-term work appeared in the form of increases in body temperature and increased circulating norepinephrine. A second very relevant and practical characteristic of this group of subjects was their susceptibility to even very mild levels of acute hypoxia during heavy work. For exam-

ple, simulation of 7,000 to 8,000 ft altitude caused PaO_2 to drop into the low to mid 40s, simply because the hyperventilatory response was inadequate--and this rather severe hypoxemia was developed even within the first 30 sec of heavy exercise (see Fig. 1B). Finally, an extensive comparison with the literature did reveal some reports of healthy subjects achieving significant hypoxemia in heavy work (see Figs. 2A and 2B). Further, the subjects and a number of our subjects were clearly showing this trend toward development of hypoxemia even at relatively low VO_2s (i.e. ~3.5 L,min VO_2).

B. In many of our most hypoxemic subjects little or no hyperventilation was shown, as metabolic acidosis and hypoxemia developed either over time of exercise (Fig. 3) or from one exercise load to the next. We determined that neither the level of chemical stimuli (PaO_2 and [H+]) nor the magnitude of ventilatory response to imposed hypercapnia or hypoxia, per se, (as determined at rest) provided explanations for this lack of hyperventilatory adaptation or the variations in exercise ventilatory response among individual subjects. Hypoxemia during exercise was also shown to dramatically increase the level of circulating catecholamines--especially norepinephrine--over the time-course of 3 to 5 min of heavy exercise. This was shown by either relieving the hypoxemia of (air-breathing) exercise with high oxygen breathing or helium breathing or by inducing (more) hypoxemia by lowering inspired O_2. These changes in adrenergic amines present yet another potent source of the hyperventilation usually achieved during hypoxic exercise, but in this case even the presence of these interactive stimuli elicited little compensatory hyperventilation.

This is just further evidence to confirm our previous concept that, indeed, some mechanical constraint probably played a significant role in determining the hyperventilatory response. We further examined this premise in two sets of studies, one aimed at determining pulmonary pressure--and flow--limitations in short-term heavy exercise (see C below) and the other concerned with the effects of "loading" and "unloading" the respiratory muscles on inspiratory "effort" or "drive" (see D below).

C. Evidence of Exercise Loading of the Respiratory Muscles in Heavy Exercise in Hypoxia. Five fit, but not highly trained, subjects were examined during mild to very heavy levels of short-term bicycle ergometer exercise while breathing air and again while breathing low F_IO_2 (0.12 to 0.17), helium, and then combinations of helium and low oxygen. Esophageal and gastric balloons were in place and at rest we determined the maximum flow-volume curve and maximum transdiaphragmatic pressures and maximum breathing capacity (for 15 sec). Thus far several of our findings point to the occurrence of excessive flow-resistive work and perhaps even diaphragmatic fatigue during heavy exercise in hypoxia.

1. In normoxia at maximum exercise, expiratory and inspiratory portions of the tidal flow-volume curve met or slightly exceeded the loops achieved with maximum FVC at rest. Maximum inspiratory esophageal pressures during tidal breathing occasionally exceeded 30 cm H_2O and approached mximum inspiratory pressure, but this occurred only at very peak exercise levels. $P_{di}max$ occasionally showed 10 to 20% decrements following maximum work but these were

not consistent among or within subjects. (On one occasion we performed a force:frequency curve for the diaphragm before and after exhaustive normoxic exercise, whereby the phrenic nerve was stimulated [at the base of the neck] at constant voltage and over the range of 10 to 100 Hz. The 15% decrement in this subject in $P_{di}max$ was matched by an equivalent decrement in P_{di} at all stimulation frequencies). We have these lines of evidence that 20 to 30% reductions in FRC occurred consistently with heavy exercise: (a) inspiratory capacity was consistently reduced; (b) end-expiratory esophageal pressure was consistently reduced; and (c) on a few trials we showed that the helium-oxygen rebreathing FRC was reduced, but these latter results were highly variable, mainly because of the difficulty of performing rebreathing techniques in very heavy work.

2. In <u>hypoxia</u> (0.12 F_IO_2 and SaO_2 75-80%) at all exercise loads > 80% max VO_2, the tidal breath flow-volume loop matched or exceeded both inspiratory and expiratory limits of the FVC (V_E and breathing frequency both were increased 10-20% > normoxia). Further, at near maximum hypoxic exercise the inspiratory portion of the pressure-volume curve frequently equaled that achieved with maximum voluntary effort as peak inspiratory pressures exceeded 30 to 35 cm H_2O. The magnitude of these negative swings in pleural pressure during heavy hypoxic exercise also approximated those achieved in the inspiratory phase of the MBC maneuver--although the latter was at higher lung volumes. $P_{di}max$ showed a 20 plus percent reduction following exhaustive hypoxic exercise in three subjects.

3. <u>Helium breathing</u> expanded the limits of the maximum flow-volume and pressure-volume loops by 15 to 25%. Thus even though V_E, frequency, flow, and pleural pressures were increased substantially during heavy exercise with helium breathing, the pressures developed were always within their maximum "limits" at any given lung volume. After trials with combined helium-hypoxia showed that ventilation during heavy exercise was only minimally affected (<10%) by the addition of low oxygen.

D. <u>Load Compensation as An Important Contributor to Inspiratory "Drive" During Exercise</u>. One study has been almost completed and another one about half completed, both directed toward this question. First we studied five subjects over a wide range of work loads (very mild to maximum) on the bicycle ergometer with very small (100 kpm) increments in load every two minutes--first while breathing room air and then with helium (0.79 He:21 O_2). We did repeat trials using various combinations of work loads with intermittent rests to achieve the most reproducible steady state values at each work load. Breath-by-breath measurements were made of V_E, f, V_T, T_I, T_E, and of esophageal, gastric, and transdiaphragmatic pressures. Inspiratory "effort" or drive was measured breath-by-breath using the differentiated mouth pressure dp/dt_{max} (see Skatrud, Dempsey & Kaiser, 1978) and during 20 sec of each work load by repeated trials of mouth occlusion pressure, $P_{0.1}$. (Theoretically, $P_{0.1}$ [and dp/dt_{max}] provide good indices of inspiratory "neural" drive, but may be affected by changes in FRC [<u>i.e.</u> resting length of the respiratory muscles]. Our preliminary data do show some decrease in FRC with exercise).

To date, the important findings are as follows (see Figs. 4A and 4B). $P_{0.1}$, V_E, and V_T/T_I all increased curvilinearly with increasing exercise during air and helium breathing, especially as relative work intensity exceeded about two-thirds maximum. During air-breathing, the increase in $P_{0.1}$ consistently exceeded that in V_E or V_T/T_I so that the ratios of $P_{0.1}/V_E$ and $P_{0.1}/V_T/T_I$ showed steady increase with increasing work and these increases were evident even at relatively moderate work loads (~40 to 60% max VO_2). Helium breathing completely removed this disassociation of inspiratory effort to ventilatory output as the ratios of $P_{0.1}/V_T/T_I$ and $P_{0.1}/V_E$ were slightly lower than those during room air breathing at the very low work loads and--more importantly--showed no increase with increasing work load--even at very high work intensities. Thus, "effective" inspiratory impedance increases during air-breathing exercise due in part to increasing breathing frequency and mainly due to increases in the mechanical time-constant of the respiratory system (resistance x compliance). Helium breathing "unloaded" the pulmonary system, reduced effective impedance, and prevented its increase during exercise. We are currently analyzing the data in terms of total ventilatory work, resistance, and dynamic compliance to quantify these exercise--and gas density--induced changes in impedance.

We believe these data to have significant implications for ventilatory control during air-breathing exercise--even moderate exercise. First the ventilatory response does not represent a full expression of inspiratory "drive" as mechanical impedance has "constrained" or limited ventilatory output. In turn, the "excessive" inspiratory effort during exercise probably represents a "load compensation" response to the increased impedance. Clearly V_E (or V_T/T_I) cannot be considered a valid index of inspiratory drive even in the healthy person during moderate exercise. In situations where even additional afferent inputs are involved during exercise such as hypoxia, we could predict, based on our older data (Thoden et al., 1969), even greater increases in impedance, constraint of ventilatory response and augmented load compensation. These studies are currently underway.

We are also currently examining another way of explaining this idea of "load" compensation and impedance during exercise. We measure breath-by-breath transient changes in inspiratory "drive", V_E and timing; in P_{di}, esophageal pressures, resistance, compliance, and total work; and in end-tidal gases and end-expiratory lung volume, in response to fast (with a breath) changes in inspirate gas density (He and SF_6). These studies are being conducted in heavy and light exercise and in normoxic and hypoxic backgrounds. Our idea here is that the initial breath--following a step change in the inspirate gas density--will represent the immediate response of the respiratory muscles to loading (or unloading) and the "later" response (beyond breath 3 or 4) will show reflex effects and/or the effects of (measured) breath-by-breath changes in chemical stimuli ($P_{ET}CO_2$ and O_2). The valve circuit for fast changes of inspirate has been built, and we have completed studies in four subjects under all conditions of work load and gas densities. With this transient analysis we can clearly see the reduced inspiratory effort associated with "unloading" (He) and the increased effort (or drive) associated with loading (SF_6) as these effects occur on the first breath of the load change. Changes

in $P_{ET}CO_2$ are evident within a few breaths after this initial response and serve to modify the original load response. Thus the changes in $P_{0.1}$ we observed in the steady-state of exercise with unloading, substantially underestimate the actual magnitude of the compensatory load response, because of negative feedback from chemical stimuli (hypo- or hyper-ventilation). These data are still in the analysis stage.

II. Exercise and Chronic Hypoxia Studies of Respiratory (and Locomotor) Muscles in Rats.

A. We finally finished our descriptive analysis of the ventilatory response and arterial blood acid-base regulation in the exercising rat. The data were presented at FASEB and the manuscript recently submitted for publication (see enclosed, Fregosi & Dempsey). The chronically catheterized rat proved to be a highly suitable model for our studies. We showed a hyperventilatory response to exercise as $PaCO_2$ fell with each increment in metabolic rate. This hyperventilation was shown not to be due to temperature changes or [H+] (in mild exercise) and was critical to [H+] homeostasis and maintenance of PaO_2 in heavy work.

B. Concerning exercise effects on respiratory and limb muscle metabolic acids, glycogen, and high energy phosphates. We have collected all muscle samples (via our freon in vivo freezing technique) with simultaneous blood sampling at rest and during five short-term exercise loads, from mild intensity to beyond max VO_2. This required our study of 80 animals. These tissues are still being assayed--but some initial data confirms our pilot findings that the diaphragm shows lactate accumulation and glycogen depletion at about the same rate and magnitude as limb muscles (of similar mixed fiber-type composition) and even during rather moderate to moderately heavy exercise. Similar studies of long-term heavy exercise in hypoxia will begin as soon as we can choose the relative work load to use for such exercise based on the results of our muscle metabolite assays obtained from our short-term work studies.

A few technical problems occurred in our studies which considerably delayed our progress, but were instructive. First we determined that "useful" muscle samples, to reflect the exercise effects, must be obtained within the initial minute following exercise and this was possible only if we used one animal for the respiratory muscles and another for the limb muscles. We also determined that in vivo freezing (as opposed to excision and then freezing) was absolutely necessary for obtaining realistic values for high energy phosphates in the exercising animal. Finally, we tested a commonly used technique for muscle tissue pH which uses a tissue homogenate measured directly with the pH electrode. The major problem here is that almost all of the tissue CO_2 is liberated with this technique--thus when we acutely loaded rats with 10% F_ICO_2 we saw no change in tissue pH. Obviously the technique is merely measuring the metabolic acid determinant of tissue [H+]. Since we already measure metabolic acids, we have abandoned this technique.

C. Chronic hypoxic effects on muscle morphology, oxidative capacity, and metabolic acids and high energy phosphates. These studies are being done in cooperation with Dr. Robert Fitts of Marquette University who is determining muscle fiber type. In the normal (sea-level) animal we found--as has been reported in the cat--a marked heterogeneity of fiber types throughout the diaphragm and even within cural and costal portions of the diaphragm. A further unique (preliminary) finding here is that the correlations of fiber-type seems quite different between the abdominal vs thoracic side of the diaphragm, even in a diaphragm as thin as that in the rat. We have exposed 25 rats for 3 weeks to 6600 m altitude. Substantial hyperventilation occurred (near $PaCO_2$ = 17 mmHg) at this severe level of hypoxemia (PaO_2 ~ 30 mmHg), pH was alkaline but about two-thirds compensated, and a substantial polycythemia occurred by the third week (H'ct 60% plus) which brought arterial O_2 content within 20% of sea-level values. Following chronic exposure we housed the animals in a glove box apparatus (F_IO_2 = 0.08) from which we could extract the animals one at a time for purposes of obtaining limb and respiratory muscles. Assays are currently being done for fiber type, oxidative capacity (citrase synthase activity) and high energy phosphates, metabolic acids, and glycogen. Once these assays are complete we plan to investigate similar effects at a lower altitude (4300 m)--if warranted--and to examine these effects of chronic hypoxia in the acutely exercising animal and in the animal who combines physical training in hypoxia.

III. Mechanism of Periodic Breathing in Hypoxia Sleep--Humans

A. We have now completed our study and analysis of the role of chemoreceptor stimuli in the production of periodic breathing during hypoxic sleep and the data are summarized in two original publications (Berssenbrugge et al., in press; Skatrud et al., in press) and two symposium proceedings publications (in press) (see enclosures). Fig. 5 summarizes our view of a model to explain periodicity on the basis of: (1) an apneic threshold very sensitive to hypoxic-induced reductions in $PaCO_2$ to the extent that apnea occurs even when $PaCO_2$ during slow-wave sleep is equal to $PaCO_2$ during wakefulness, i.e. 38-41 $PaCO_2$ in a given subject; and (2) a curvilinear hypoxic response so that during the hypocapnic-induced apneic period the position on the hypoxic response moves to higher gain, causing an augmented drive to breathe, ventilatory overshooot on the subsequent breaths following the apnea, more hypocapnia, apnea, etc. This phenomena is confined to non-REM sleep. The original views of Cherniack and co-workers form an important basis of this hypothesis.

B. We also completed our analysis of the effects of duration of hypoxic exposure--up to 4 days-- on periodic breathing during sleep (Berssenbrugge et al., submitted) (see enclosed manuscript). To summarize, we found variable effects of acclimatization. None of the 5 subjects worsened their number or length of apneas or decreased their degree of periodic breathng; despite the considerably lower levels of $PaCO_2$ they achieved with acclimatization. The reason for this resides in the fact that the apneic threshold to hypocapnia during non-REM sleep depends critically on the level of "background" stimulation. For example, we previously showed (in imposed positive pressure hyperventilation studies during sleep) that increasing the prevailing

stimulus with a few minutes of hypoxia significantly decreased the PCO_2 necessary to produce apnea and hyperoxia increased the PCO_2 at which apnea occurred. With long-term hypoxia the "acclimatization factor" became the crucial "background" drive which prevented more apnea and periodicity from occurring despite more hypocapnia. This additional background drive in chronic hypoxia would also explain why treatments with ventilatory stimulants such as carbonic anhydrase inhibition and/or medroxyprogesterone were previously shown to alleviate periodic breathing during sleep in the sojourner to high altitude. A second important finding here was that three of the five subjects experienced much less periodic breathing from night 1 to night 4 at 4300 m; in fact, the number of apneas in two of the subjects was greatly reduced to the point where their breathing was only borderline "periodic." This decline in periodicity was obvious by night 2 in these subjects. The remaining two subjects remained as periodic on night 4 as they had been on night 1. We found no obvious explanations for these differences among subjects.

C. Ventilatory acclimatization, i.e. the time-dependent increase in ventilation with duration of hypoxic exposure, was not affected by "state." That is, the increase in alveolar ventilation and development of hypocapnia which occurred over 4 nights at 4300 m was identical while awake and during non-REM or REM sleep. These negative findings imply that suprapontine influences on ventilatory control--which attend wakefulness and are removed or greatly depressed in non-REM sleep--probably have little or no mediating influence on the time-course or magnitude of ventilatory acclimatization or deacclimatization. This contradicts hypotheses previously suggested by ourselves and by Tenney & Ou from their studies on decerebrate and decorticate cats.

D. We examined the influence of the ventilatory sensitivity to hypoxia on the magnitude of periodic breathing during sleep. We found no correlations whether the hypoxic "sensitivity" was determined during sleep or wakefulness or during acute or chronic hypoxia. This differs from Lahiri's recent contention from the American Himalayan expedition that the lack of periodic breathing in the Sherpra at high altitude was due to his "blunted" hypoxic response. These data remain highly suspect because no EEG sleep staging was documented, i.e. perhaps the Sherpra merely experienced more REM sleep in hypoxia. Nevertheless, the differences between our findings and their's might suggest that very large differences in acute hypoxic response might have to exist (10 to 12 times in Sherpras vs sojourners vs 3 to 5 times among our sojourners) before they have any predictive value regarding periodic breathing during sleep in hypoxia.

E. Finally, we began to examine the feasibility of a "threshold" of hypoxia at which periodic breathing first appeared. We have concluded that frank periodic breathing requires a sufficient level of hypoxemia and sufficient time in hypoxia (>10 to 15 min) for enough hypocapnia to occur to push the subject below his own apneic threshold. However, this is much to simplified a view as even though no obvious, measureable apneas are occurring, a predictable recurring "cycling" of breathing pattern starts to occur at fairly mild levels of hypoxia. To detect the onset of this "instability" in breathing pattern requires another type of computer analysis, i.e. cross-correlation

analysis, which we are now just beginning to apply to our data.

IV. Publications Supported All or in Part By Contract No. DAMD 17-82-C-2259 (Previously DAMD 17-77-C-7006), Contract Year 06 (October 1, 1982 to August 1, 1983)

A. MANUSCRIPTS PUBLISHED OR IN PRESS

1. McCrimmon, D.R., J.A. Dempsey, and E.B. Olson, Jr. The effects of catecholamine depletion on ventilatory control in normoxic and hypoxic rats. J. Appl. Physiol. (in press).

2. Olson, E.B., Jr., E.H. Vidruk, D.R. McCrimmon, and J.A. Dempsey. Monoamine neurotransmitter metabolism during acclimatization to chronic hypoxia. Respir. Physiol. (in press).

3. Berssenbrugge, A., J. Dempsey, C. Iber, J. Skatrud, and Olson. Mechanisms of hypoxia-induced periodic breathing during sleep in humans. J. Physiol. (London) (in press).*

4. Skatrud, J.B., and J.A. Dempsey. Interaction of sleep state and chemical stimuli in sustaining rhythmic ventilation. J. Appl. Physiol. (in press).

5. Jameson, L.C., C.A. Smith, and J.A. Dempsey. A method for cisterna magna perfusion of synthetic CSF in the awake goat. J. Appl. Physiol. (in press).

6. Musch, T.I., J.A. Dempsey, C.A. Smith, G.S. Mitchell, and J.A. Dempsey. Metabolic acid production and pH regulation in brain tissue during acclimatization to chronic hypoxia. J. Appl. Physiol. (in press).

7. Dempsey, J.A., G. Mitchell, and C. Smith. Chemoreception during exercise. NIH Workshop on Exercise in Health and Disease, September 1981. Am. Rev. Respir. Dis. (in press).

8. Berssenbrugge, A., J. Dempsey, and J. Skatrud. Nature and mechanisms of periodic breathing. APS Symposium on Man at High Altitude, San Diego, CA, October 1982 (in press) (S. Lahiri and J. West, editors).

9. Dempsey, J.A. Ventilatory control during sleep in hypoxia. Hypoxia Symposium III, Banff, Canada, January 1983 (J. Sutton and C. Houston, editors) (in press).

10. Dempsey, J., J. Skatrud, and E.B. Olson, Jr. Role of hormones in ventilatory control. Handbook of Physiology-Respiration (in press).

B. MANUSCRIPTS IN REVIEW PROCESS

1. Berssenbrugge, A., J. Dempsey, and J. Skatrud. Effects of sleep on ventilatory acclimatization to chronic hypoxia (submitted to J. Appl. Physiol.)*

2. Dempsey, J., P. Hanson, and K. Henderson. Exercise-induced arterial hypoxemia in healthy persons at sea-level [submitted to J. Physiol. (London)]*

3. Smith, C.A., L.C. Jameson, G.S. Mitchell, T.I. Musch, and J.A. Dempsey. Central-peripheral chemoreceptor interaction in the awake CSF-perfused goat. J. Appl. Physiol. (accepted for publication).

C. ABSTRACTS

1. Fregosi, R., H. Hoff, G. Staffeld, and J. Dempsey. Arterial blood acid base status and respiratory muscle metabolites during exercise in rats. Fed. Proc. 42(3):2585, 1983.

2. Dempsey, J., C. Smith, T. Musch, J. Skatrud. Changing role of CNS [H+] as a ventilatory stimulus in various physiologic states. New Zealand Med. J. (in press).*

* These studies are particularly relevant to current aims of the contract and a copy of the manuscript is appended.

V. Military Significance

Our contract work is aimed at a better understanding of two physiologic problems occurring in hypoxic environments which clearly effect the well-being and performance capabilities of the human sojourner at high altitudes. These problems are periodic breathing during sleep leading to loss of quality sleep and the resulting daytime hypersomnalence and fatigue; and the regulation of the ventilatory response and pulmonary gas exchange during exercise in hypoxia which are key determinants of exercise performance.

Our work on periodic breathing during hypoxic sleep provides the first comprehensive, quantitative description of this problem and provided the first definitive evidence detailing the major causes of periodicity and the reasons behind the beneficial effects of acute O_2 administration. Further, our more recent data suggests that acclimatization over a matter of a few days at high altitude may greatly alleviate periodic breathing during sleep. However, this remains a highly individual characteristic which we were unable to predict from available measurements. Indeed, the test of acute hypoxic ventilatory response--which is commonly used as a predictor of many facets of acclimatization--had no predictive value at all for the occurrence or severity of periodic breathing in hypoxic sleep.

Exercise capacity as determined by the pulmonary system in hypoxia and the debilitating symptoms of dyspnea which accompany exercise in hypoxia have been the subject of our investigations. Our work has detailed the critical limitations to oxygen transport presented by the failure of the lung's gas exchange and ventilatory control system and chest wall mechanics to respond adequately and/or efficiently to heavy work in hypoxic environments. Further, the baseline work in normoxic environments clearly shows the susceptibility of some highly fit individuals to these problems during exercise, thereby providing a basis for prediction of problems with high altitude exercise from measurements made at sea-level. We also showed the simple use of exercise tests in acute hypoxia--even using non-invsive

measurements of arterial O_2 saturation--should provide excellent prediction of gas exchange "failure" at high altitudes. Our recent findings also strongly implicate a highly significant role for pulmonary and chest wall mechanics in the regulation of ventilation--and thus of gas exchange--during exercise--especially hypoxic exercise. We would predict with some confidence that the sea-level native with even "mild," asymptomatic airway disease (such as that due to chronic cigarette smoking or the mostly reversible airway disease of the otherwise healthy asthmatic) will have substantial problems in maintaining arterial oxygenation and/or avoiding extreme dyspnea during exercise at even mild elevations in altitude.

VI. Facilities and Personnel

No changes were made in the past year.

TABLE 1. Effects of Duration of Exercise and Ventilatory Response on PaO_2 in a Single Subject

	$\dot{V}O_2$ (L,min %Max)	$PaCO_2$ (mmHg)	P_AO_2 (mmHg)	PaO_2 (mmHg)	A-aDO_2 (mmHg)	$\dot{V}_E$ (L,min)	Freq. (min)
Treadmill Run 4 min	2.5-57%	42	95	68	27	55	52
Road Race* 80 min	2.9-66%	30	113	87	26	120	75

* The road race data was summarized from previously reported data in Subject S.A. (Hanson et al., 1982), based on nine sets of measurements made over the course of a 23-km road race which lasted 89 minutes. $PaCO_2$ ranged from 29 to 33 mmHg and PaO_2 from 90 to 79 mmHg.

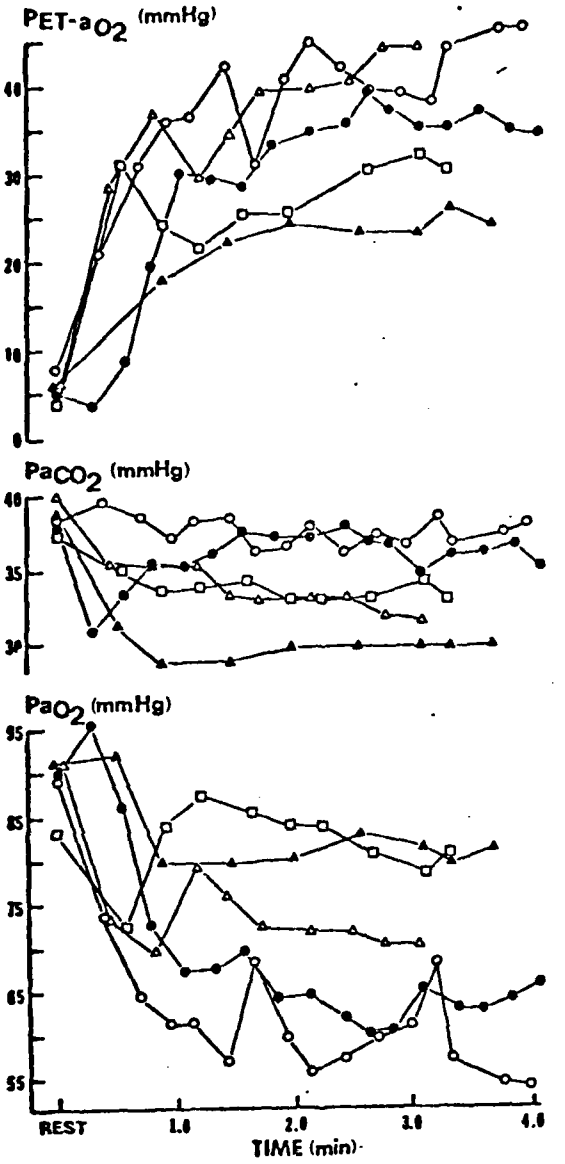


Figure 1A. Effects of heavy exercise (85-95% $\dot{V}O_2$ max) breathing air on arterial blood gases and A-aDO_2 in 5 runners.

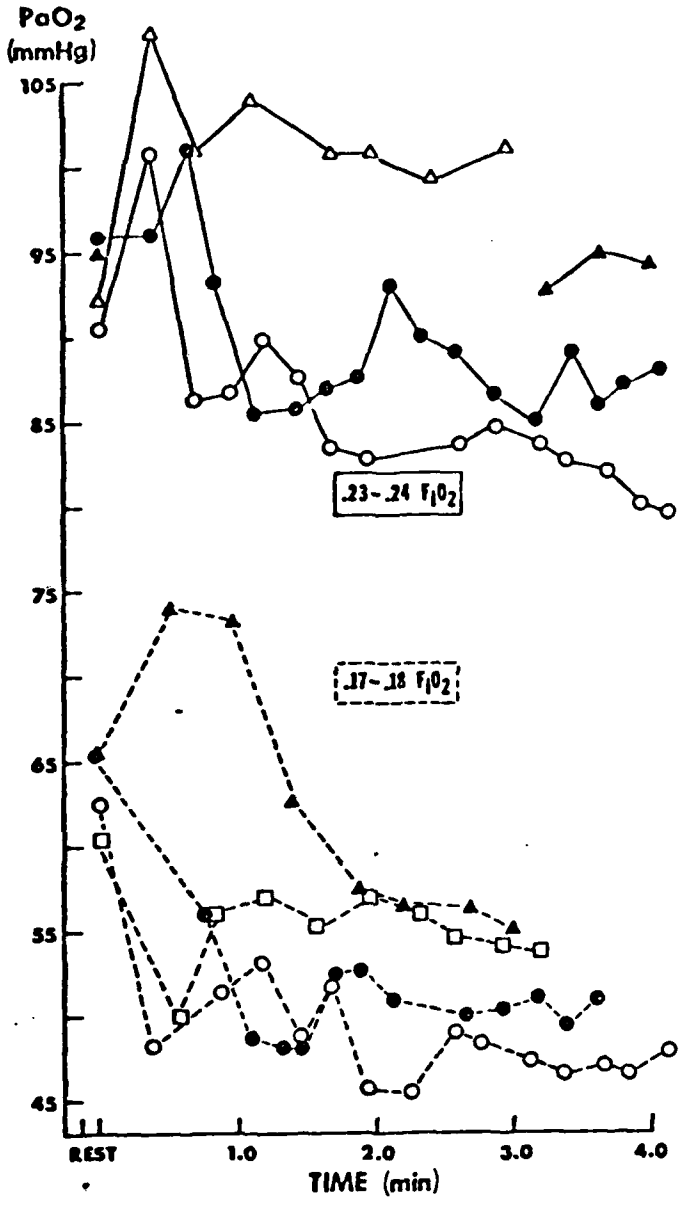


Figure 1B. Effects of breathing mildly hyperoxic and mildly hypoxic gas mixtures on PaO_2 during heavy exercise.

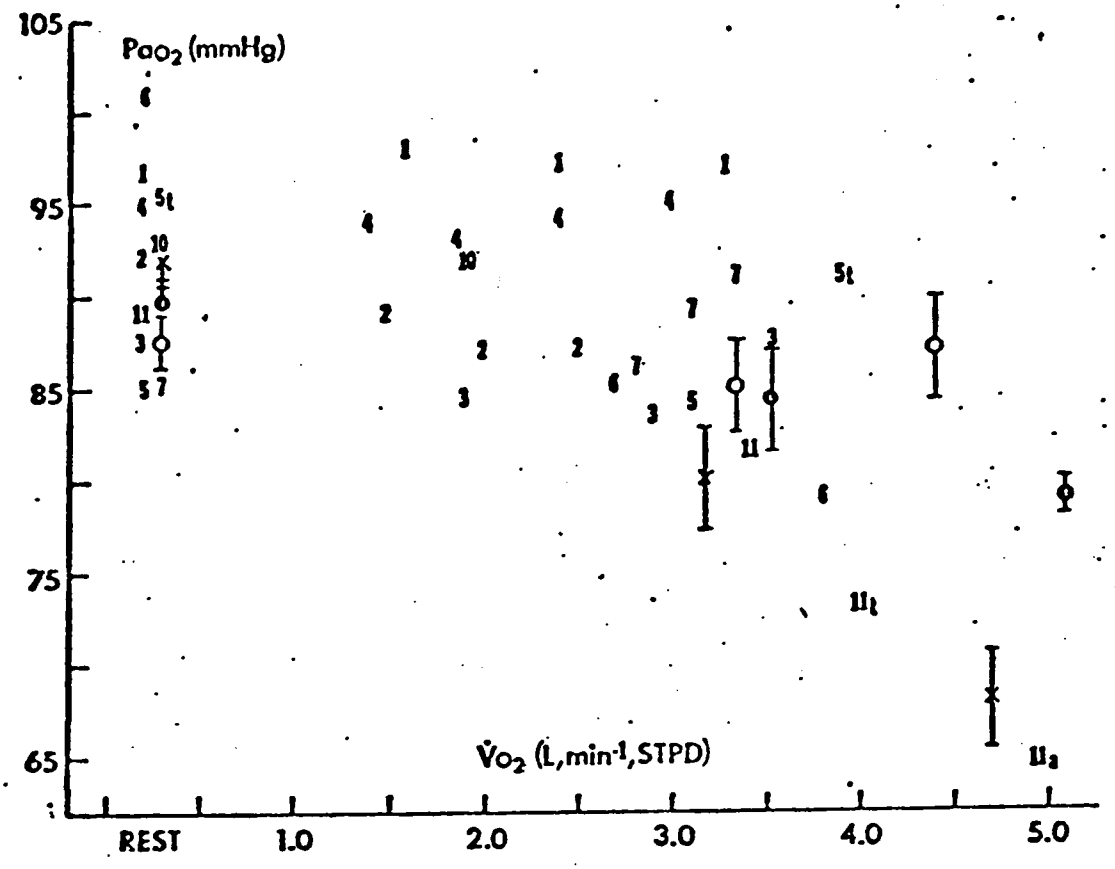


Figure 2A. Effects of steady-state exercise of varying intensity up to maximum $\dot{V}O_2$ on arterial PO_2 in healthy, young adult male subjects in normoxia. Mean values from the literature: 1. Whipp & Wasserman, 1969, N = 5; 2. Dempsey et al., 1966, N = 12; 3. Asmussen & Nielsen, 1960, N = 13; 4. Dempsey, Reddan, Rankin, Birnbaum, Forster, Thoden & Grover, 1971, N = 10; 5. Saltin et al., 1968, N = 5; (5 = control, 5_t = after training); 6. Holmgren & Linderholm, 1958, N = 13 ($\dot{V}O_2$ was estimated from the reported kpm external work loads); 7. Mitchell, Sproule & Chapman, 1958, N = 24; 8. Jones, McHardy, Naimark & Campbell, 1966, N = 7; 9. Harris, Seelye & Whitlock, 1976, N = 8; 10. Gledhill et al., 1978, N = 5; 11. Rowell et al., 1964 (control = 11 and after training = 11_t, N = 4; and trained athletes = 11_a, N = 4). For #11 mean PaO_2 values estimated from reported SaO_2 using the mean max pH and temperature from the present study. Three groups from the present study are also shown (mean ± SEM) at one submaximal work load and at Max $\dot{V}O_2$. o and • (N = 4 each) and x (N = 8).

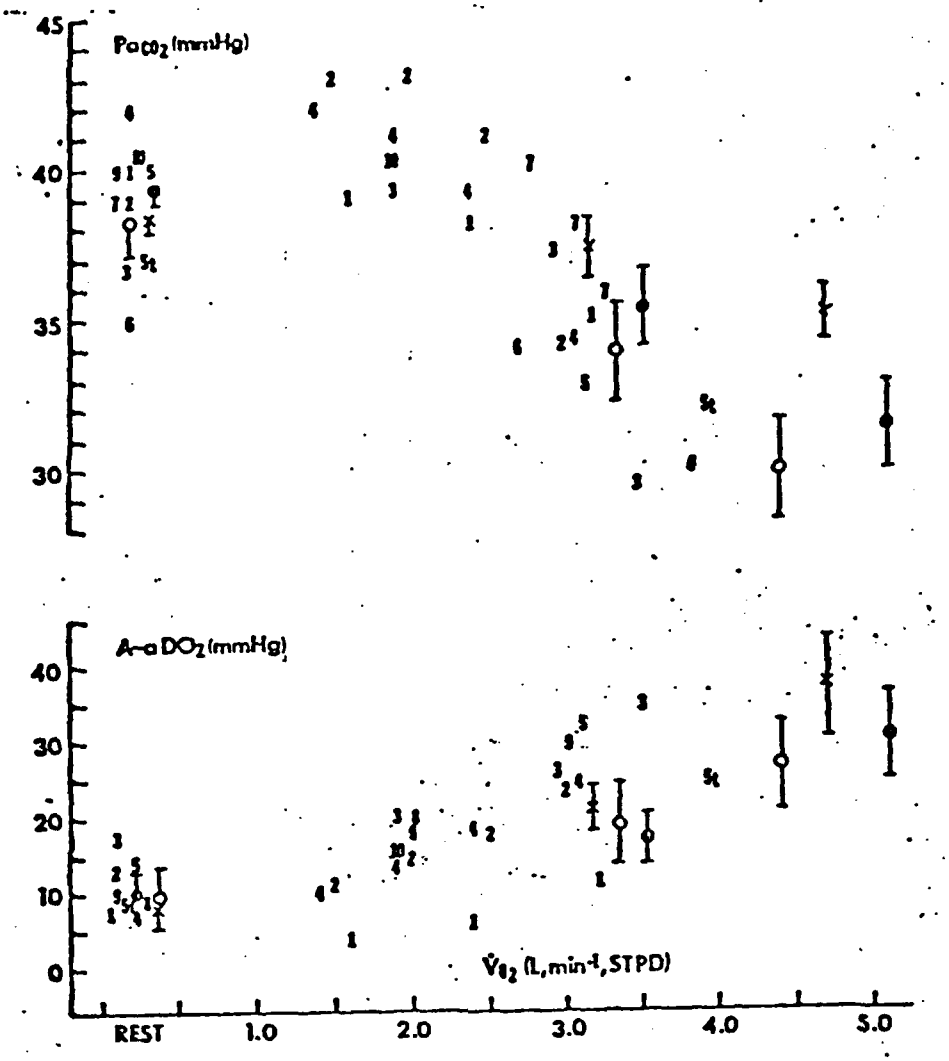


Figure 2B. Effects of steady-state exercise of varying intensity up to maximum $\dot{V}O_2$ on arterial $PaCO_2$ and A-aDO_2. Mean values from the literature and from three groups in the study. See legend to Figure 2A.

Fig. 3

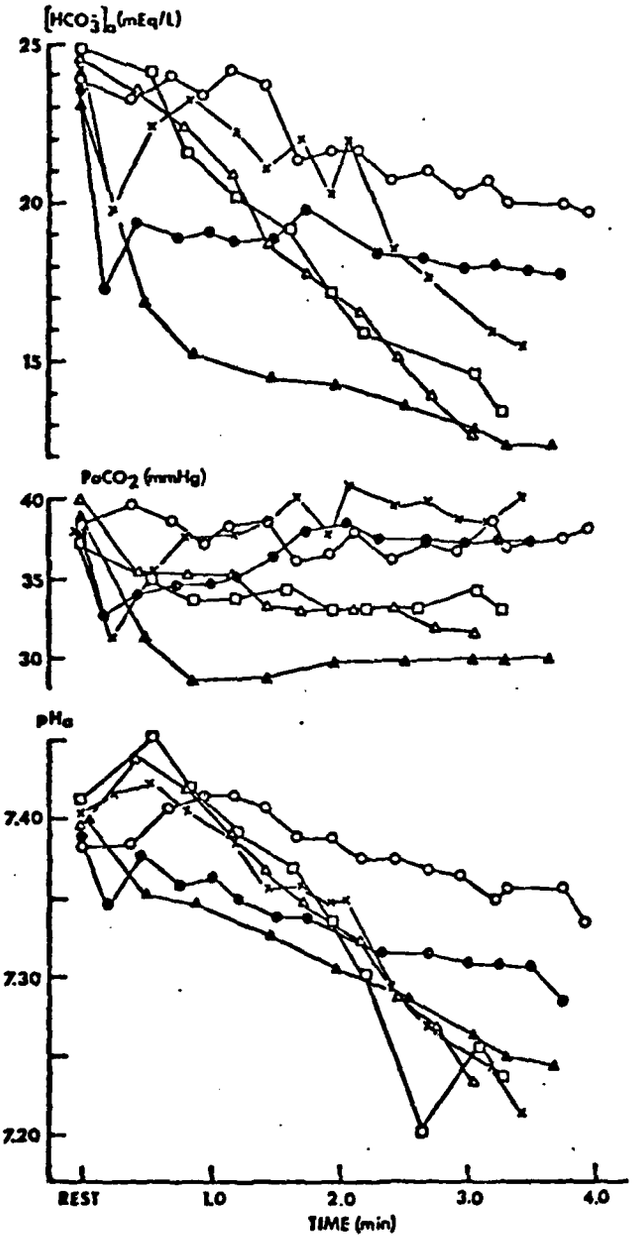


Figure 3. Arterial acid-base status over the time-course of heavy exercise (corresponding PaO_2s are in Figure 1A).

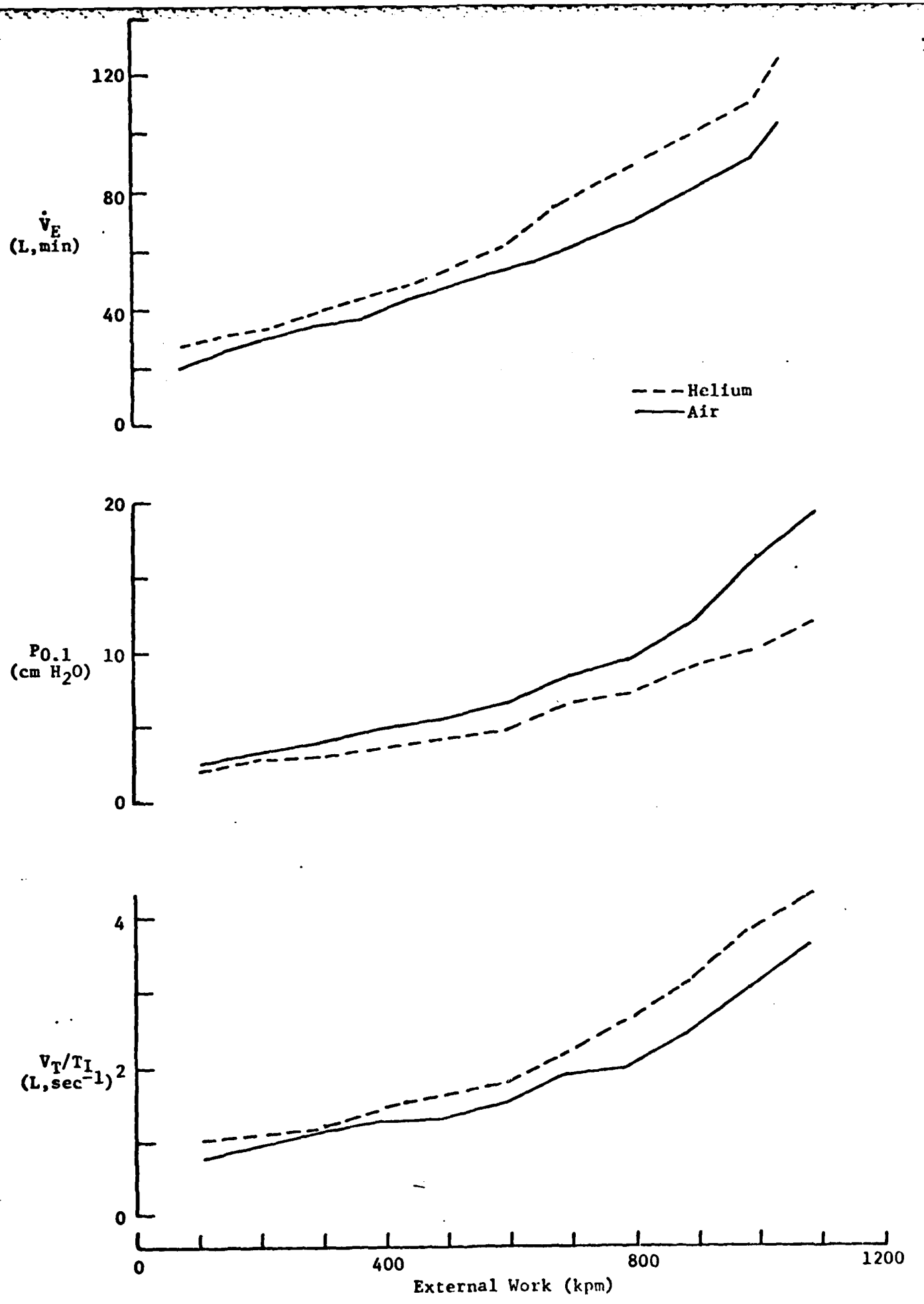


Figure 4A. Exercise effects while breathing Air vs He on $\dot{V}_E$, mean inspiratory flow (V_T/T_I) and inspiratory effort or "drive" ($P_{0.1}$) during incremental exercise of 2 minutes per work load (mean values, N = 5).

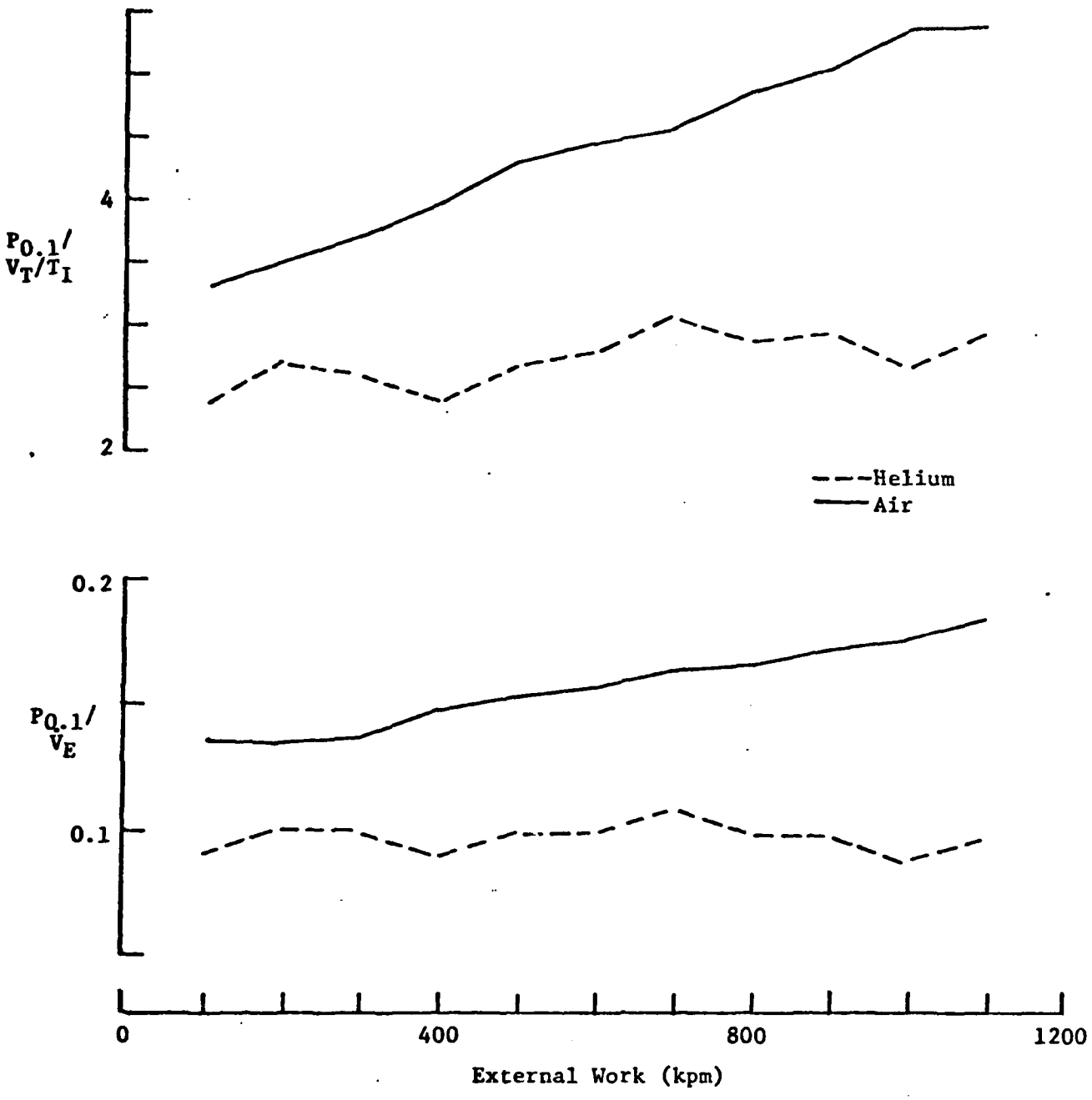


Figure 4B. Exercise effects while breathing Air vs. He on ratios of inspiratory flow to inspiratory flow and inspiratory effort to V_E.

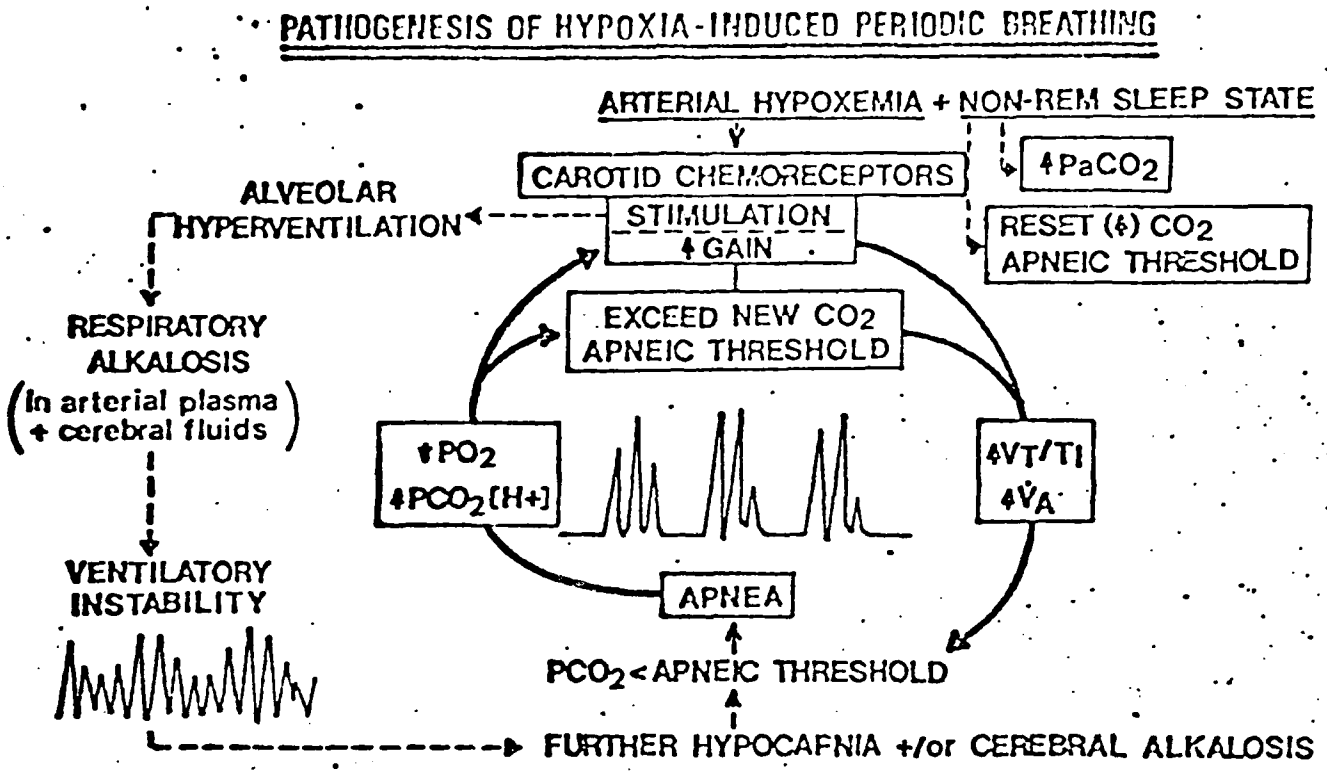


Figure 5. Schematic model of the pathogenesis of periodic breathing during sleep in hypoxia. Non-REM sleep causes alveolar hypoventilation and a "resetting" of the apneic threshold so that >2 to 5 mmHg of hypocapnia causes apnea of 5 to 40 seconds duration. Arterial hypoxemia causes hyperventilation via carotid chemoreceptor stimulation leading to hypocapnia and then (>10 to 15 minutes of hypoxemia) to ventilatory "instability." An additional pertubation--i.e. change in airway resistance, a "sigh" or other type of hyperinflation, or maybe even just more hyperventilation with a longer time in hypoxia--leads to more hypocapnia with sufficient CNS alkalosis to cause apnea. During the apneic period, PaO_2 falls to the steeper, "higher gain" portion of the hypoxic response curve, $PaCO_2$ rises causing both a right-shifted higher gain hypoxic response curve and (finally) the CO_2 apneic threshold is exceeded. The very high "new" gain of the control system causes a large ventilatory response for 2 or 3 breaths sufficient to drive $PaCO_2$ again below the apneic threshold--and the periodicity continues.

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